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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,711	12/14/2001	Ramesh Patel	HA724 NP	5245
23914	7590	01/06/2004	EXAMINER	
STEPHEN B. DAVIS BRISTOL-MYERS SQUIBB COMPANY PATENT DEPARTMENT P O BOX 4000 PRINCETON, NJ 08543-4000			WEBER, JON P	
			ART UNIT	PAPER NUMBER
			1651	

DATE MAILED: 01/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/017,711	PATEL ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 November 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-10 and 15-20 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-10 and 15-20 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
    Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
    Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
    a) ☐ All    b) ☐ Some \*    c) ☐ None of:  
        1. ☐ Certified copies of the priority documents have been received.  
        2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
        3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
    a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____  |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                 | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>4/02, 10/02</u> | 6) <input type="checkbox"/> Other: _____                                    |

*Status of the Claims*

The response with amendments filed 03 November 2003 has been received and entered. Claims 1-10 and 15-20 have been presented for examination.

*Election/Restrictions*

Applicant's election of Group I, claims 1-10 and 15-20 in Paper filed 03 November 2003 is acknowledged. The traverse argues restriction groupings that were not made between the two different methods: I - claims 1-8, 10 and 15-20, and II - claim 9. No other alleged errors in the restriction requirement were identified. Simultaneously, the non-elected claims, 11-14, were canceled. Accordingly, the election has been treated as effectively an election **without** traverse (MPEP § 818.03(a)). No further action is necessary on this matter.

*Specification*

The disclosure is objected to because of the following informalities:

At page 6, line 14 of the disclosure it would appear that the structure is incorrect, consistent with the amendments to the specification and claims made in the response of 03 November 2003.

Appropriate correction is required.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-9, 15, 17 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 9 recite "Ar refers to an aromatic or heteroaromatic ring with 5-6 carbons and one to two heteroatoms selected from O, N or S," which is confusing because it is not understood how the aromatic ring could have heteroatoms and not be heteroaromatic. Perhaps the claim should clearly indicate that it is only the heteroring that has the heteroatoms.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Pohl et al. (1997).

Pohl et al. (1997) disclose that PhAcOZ blocked amines of peptides can be removed by the action of penicillin G acylase (page 6704, column 2, and Scheme 5). While it is clear that the action of the enzyme is to remove phenacyl group allowing subsequent decomposition to give the free amine rather than direct cleavage of the urethane linkage, the instant claims merely

require the action of the enzyme to release the free amine. The structure of PhAcOZ is within the scope of the blocking group of claims 1 and 9.

Claims 1-3, 7 and 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyers et al. (1975).

Meyers et al. (1975) disclose deprotecting amines of amino acids and peptides by removing benzyloxycarbonyl (CBZ) with trypsin. D and L isomers are distinguished.

#### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-4, 7-10 and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pohl et al. (1997) and Meyers et al. (1975) in view of Williams et al. (US 5,625,030), Wong et al. (US 5,981,267) and Srivastava et al. (US 5,814,616) and further in view of Robl (US 5,508,272) and Karanewsky et al. (US 5,552,397).

The teachings of Pohl et al. (1997) and Meyers et al. (1975) have been discussed above. Pohl et al. (1997) and Meyers et al. (1975) lack the full scope of amines instantly claimed.

Williams et al. (US 5,625,030) disclose that a number of amine and hydroxyl blocking groups are well known in the art (Table III) and that these are labile in that they are susceptible to enzymatic cleavage in vivo with either esterases or amidases (column 13, lines 28-39).

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Wong et al. (US 5,981,267) disclose at column 2, lines 41-51 that amine groups are readily carbamylated enzymatically with, for example, *Candida cylindracea* lipase or Subtilisin BPN' and a homocarbonate. The resulting chiral carbamate is readily deprotected (column 2, line 67). Although enzymic deprotection is not stated, by microscopic reversibility, it must be possible enzymatically.

Srivastiva et al. (US 5,814,616) disclose at column 5, lines 22-42, that amine and/or hydroxyl protecting groups well known in the art including CBZ and t-Boc, may be introduced and later selectively removed enzymatically or chemically. No enzymatic examples are provided.

Robl (US 5,508,272) disclose the chemical synthesis of the amine products of claims 15 and 16 and their importance.

Karanewsky et al. (US 5,552,397) disclose the chemical synthesis of the amine products of claims 17-20 and their importance.

A person of ordinary skill in the art at the time the invention was made would have been motivated to use just about any suitable enzymatically removable protecting group of the carbonate or urethane type with aromatic groups because such amine and hydroxyl groups are well known in the art as shown by the relied upon and cited art. Pohl et al. (1997) and Meyers et al. (1975) show that such groups are removable enzymatically from amines. Williams et al. (US 5,625,030), Wong et al. (US 5,981,267) and Srivastiva et al. (US 5,814,616) establish that the ordinary artisan is reasonably expected to be able to selectively protect and deprotect with such groups on amines and hydroxyls. The selection of one amine compound or another appears to be an arbitrary matter of experimental design choice inasmuch as the enzyme selectivity is at the protecting group side of the scissile bond. Robl (US 5,508,272) and Karanewsky et al. (US

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5,552,397) establish that the specific amines desired are known in the art and desirable to prepare.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to deprotect amines or hydroxyls containing the urethane or carbonate protecting groups enzymatically.

Other references not relied upon establish the state of the art of enzyme catalyzed deprotection of amines protected by other protecting groups.

Briggs et al. (US 5,532,149) disclose deprotecting amines by removing phthalyl groups with an amidase from *Xanthobacter agilis*.

Waldemann et al. (1994) disclose deprotecting amines by removing phenylacetate groups with penicillin G acylase.

Royer (US 4,182,654) discloses deprotecting amines by removing pyrrolidonecarboxyl groups with an aminopeptidase such as aminopeptidase M or leucine aminopeptidase.

#### ***Allowable Subject Matter***

Claims 5-6 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The prior art does not disclose an enzyme from *Sphingomonas paucimobilis* that has the ability to cleave protecting groups of claim 1. Schinner et al. (1991) disclose that *Sphingomonas paucimobilis* produces extracellular protease. Turkiewicz et al. (1999) disclose an extracellular metalloprotease from *Sphingomonas paucimobilis*. However,

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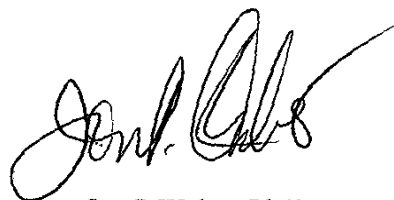
there is no evidence presented in either reference that disclosed extracellular protease can specifically cleave the protecting groups as instantly claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

My new Office room number will be Rem-03A45 and my new Office phone number will be 571-272-0925 after 15 January 2004.



Jon P Weber, Ph.D.  
Primary Examiner  
Art Unit 1651

JPW  
24 December 2003